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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/669,187	09/25/2000	Arthur M. Krieg	C1039/7035 (HCL/MAT)	2999

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1643	
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02/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/669,187	KRIEG ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *121-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *121-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/23/07;8/6/07;11/5/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05 November 2007 has been entered.

2. Claims 1-120 are cancelled.

3. Claim 121, 131 and 139-142 have been amended.

4. Claims 121-142 are under consideration.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. This Office Action contains New Grounds of Rejections.

Information Disclosure Statement

7. The Information Disclosure Statement (IDS) filed 23 July 2007, 06 August 2007 and 05 November 2007 have been fully considered by the Examiner. A signed and initialed copy of each IDS is included with the instant Office Action.

Objections/Rejections Withdrawn

8. The rejection of claims 121-124, 128-132 and 139-142 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cancer in a subject comprising administering the unmethylated immunostimulatory oligonucleotide of SEQ ID NO:246 comprising a modified backbone and a chemotherapeutic agent, does not reasonably provide enablement for a method of treating cancer in a subject comprising administering the immunostimulatory oligonucleotide of SEQ ID NO:246 and a chemotherapeutic agent, wherein the

oligonucleotide is unmethylated and lacks a phosphate backbone modification is withdrawn in view of applicants' arguments and the amendments to the claims

Response to Arguments

9. The rejection of claims 121-142 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is maintained. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 11/5/2007 states that the specification demonstrates possession of the claimed oligonucleotide genus by providing the 24 nucleotide consensus sequence that identifies (and thus is common to) all members of the claimed genus. Applicant states that the specification teaches the other species in the genus that are immunostimulatory, citing pg. 31 as disclosing SEQ ID NO:246 and a poly A or a poly T tail as well as SEQ ID Nos:262, 273, 300, 305, 352, 412, 413, 429 and 891. Applicant asserts that these sequences vary with respect to length, flanking sequence, and backbone content, yet all comprise the complete nucleotide sequence of SEQ ID NO:246 and all are taught by the specification to be immunostimulatory. Applicant states that the Examiner's reliance on Enzo Biochem and Noelle v Lederman is misplaced because the present specification provides more than one species within the claimed genus. Applicants' arguments have been fully considered but are not found persuasive. The claims still encompass an extremely large genus of immunostimulatory oligonucleotides that comprise the consensus sequence of SEQ ID NO:246 and may contain additional sequence up to 40 or up to 100 nucleotides in length of the claimed method. The disclosure of SEQ ID Nos: 262, 273, 300, 305, 352, 412, 413, 429 and 891 are not representative of the genus because SEQ ID Nos:262, 273, 300, 352, 412, 413 and 891 are identical to SEQ ID NO:246. Thus, these sequences do not comprise SEQ ID NO:246 and vary with respect to length, flanking sequence, and backbone

content. Although SEQ ID NO:305 comprises 5 additional T's at the 3' end and SEQ ID NO:429 comprises the additional sequence ttgtcgtt at the 3' end, Applicants' reliance on the description of a SEQ ID Nos:305, 429 and the generic disclosure of poly A and poly T tails are not representative of the entire genus because the genus is highly variable, inclusive to immunostimulatory oligonucleotides of varying lengths and having different chemical structures or sequences, which were not clearly disclosed or contemplated in the as filed application. Applicant has not pointed to a single immunostimulatory oligonucleotide that comprises SEQ ID NO:246 and is 35, 40, 50, 70, 90, 93, or 100 nucleotides in length and comprising just any nucleotide sequence in addition to SEQ ID NO:246 that function equivalently. Again, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one or a limited number of species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). There is insufficient written description for the subgenus of immunostimulatory oligonucleotides "comprising" up to 100 nucleotides or "comprising" 24-40 nucleotides as the as filed disclosure contains no description of the sequences contained therein and based on the limited disclosure of SEQ ID NO:246, one of skill in the art would reasonably conclude that the disclosure does not provide a representative number of species to describe the presently claimed sub-genus. Additionally, the as filed specification only discloses SEQ ID NO:246 as unmethylated and having a phosphorothioate backbone modification. Applicants reliance on a general disclosure and possibly a single species (i.e., phosphorothioate immunostimulatory oligonucleotide SEQ ID NO:246) has not provided sufficient direction and guidance to the features currently claimed. It cannot be said that

a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05

Applicant also states that the claimed combination of immunostimulatory oligonucleotide in combination with any of the recited anti cancer therapies. Applicant notes that the specification explicitly discloses carboplatin, paclitaxel, doxorubicin, cisplatin and gemcitabine and therefore, the specification provides adequate support for the combination of immunostimulatory nucleic acids with each of these anti-cancer therapies. Applicant points to various pages in the specification for support. Applicant states that support for claim 131 can be found on pg. 102, lines 9-12 and 21-23. Applicants' arguments have been fully considered but are not found persuasive. Applicants' reliance on a generic disclosure of numerous oligonucleotides and numerous chemotherapeutic agents (e.g., see pg. 15-16) does not provide adequate direction or guidance to the currently claimed limitations. The fact that carboplatin, paclitaxel, doxorubicin, cisplatin and gemcitabine are explicitly disclosed, does not provide adequate guidance or direction to selecting the claimed combination of SEQ ID NO:246 or the subgenus of immunostimulatory oligonucleotides that "comprise" SEQ ID NO:246 in combination with carboplatin, paclitaxel, doxorubicin, cisplatin, gemcitabine or even *carboplatin and paclitaxel* (e.g., carboplatin and "another cancer medicament") for the treatment of cancer as opposed to the selection of any of the other possible combinations of chemotherapeutic agents, immunotherapeutic agents or cancer vaccines disclosed. As *Ruschig* makes clear, one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention." In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure. *See id.* at 994-95, 154 USPQ at 122; *Fujikawa,* 93 F.3d at 1570-71, 39 USPQ2d at 1905; *Martin v. Mayer*, 823 F.2d 500, 505, 3 USPQ2d 1333, 1337 (Fed. Cir. 1987). With respect to claim 131, the disclosure at pg. 102 does not provide adequate written support for a method of increasing the responsiveness to a cancer therapy comprising administering an immunostimulatory oligonucleotide comprising unmethylated SEQ ID NO:246 and carboplatin and administering another cancer medicament. The disclosure of "other

cancer medicaments" would not have led the skilled artisan to administer such in combination with SEQ ID NO:246 and carboplatin. Again, where in the as filed disclosure is it contemplated that *carboplatin and another cancer medicament* were intended to be used with SEQ ID NO:246 or the subgenus of immunostimulatory sequences that "comprise" SEQ ID NO:246 in the treatment of non-small cell lung cancer?

The present application does not provide adequate written description for the subgenus of immunostimulatory sequences that "comprise" SEQ ID NO:246, or the particular combinations of said sequences and carboplatin, paclitaxel, doxorubicin, cisplatin, or gemcitabine as presently claimed from the myriad of possibilities encompassed by the broad disclosure (e.g., Table A and pp. 15-16) and there is no guidance or direction that the particular combinations presently claimed should be made rather than any of the others which could also be made. Similar to *In re Smith*, the present claims are drawn to a various subgenus's of immunostimulatory oligonucleotides that "comprise" SEQ ID NO:246 and a particular chemotherapeutic agent(s), which are not adequately supported or described in applicants' generic disclosure of an immunostimulatory oligonucleotide in combination with a chemotherapeutic agent, an immunotherapeutic agent, or a cancer vaccine (e.g., see pp. 15-16), or in the disclosure of a single or limited species, i.e., unmethylated SEQ ID NO:246 comprising a phosphorothioate backbone.

For these reasons and those already of record the rejection is maintained.

10. The rejection of claims 121-142 under 35 U.S.C. 103(a) as being unpatentable over Wagner et al (US 2004/0235778 A1, 5/14/1998) in view of Maxwell et al (Seminars in Oncology Nursing, 8(2):113-123, May 1992) is maintained.

The response filed 11/5/2007 states that the references do not teach the limitation "increasing the responsiveness to a cancer therapy" by using the claimed oligonucleotides. Applicant states that the examiners' rationale for combining the references is related to the ability of immunostimulatory nucleic acids to stimulate

hematopoiesis and the teaching of myelosuppression by certain chemotherapeutic agents. Applicants' arguments have been fully considered but are not found persuasive. In response to applicant's argument that references do not teach the limitation "increasing the responsiveness to a cancer therapy", a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Thus, as set forth in the rejection, the method for treating cancer or non-small cell lung cancer in a human patient comprising administering by injection the immunostimulatory oligonucleotide of SEQ ID NO:80 (identical to SEQ ID NO:246) in combination with one or more of carboplatin, paclitaxel, cisplatin, 5-fluorouracil and/or doxorubicin in an effective amount to treat the cancer as taught by Maxwell et al and Wagner et al, would necessarily "increase the responsiveness to a cancer therapy". The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). See MPEP 2145 II. Applicants' remarks regarding Manegold et al are acknowledged, however, it is noted that while grade 3 or 4 thrombocytopenia events were numerically more common in patents receiving SEQ ID NO:246 with chemotherapy, the only grade 4 event was in the chemotherapy alone arm. Further, Manegold teach that objective responses and median survival time were greater for patients receiving SEQ ID NO:246 with chemotherapy compared to chemotherapy alone. It is noted that Manegold is not relied upon in the instant rejection, however, it is reiterated that Wagner et al provide evidence that the combination of a chemotherapeutic agent and an immunostimulatory oligonucleotide reduces the loss of platelets compared to chemotherapeutic agent alone (see Fig. 13). Applicant is reminded that obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence

showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643